Conference paper

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Polyheterocycle-carbohydrate chimeras: photoassisted synthesis of 2,5-epoxybenzoxacines and 2,5-epoxybenzazocine scaffolds and their postphotochemical hydroxylations

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Abstract: Photoassisted synthesis of complex polyheterocyclic molecular architectures via excited state intramolecular proton transfer (ESIPT) is for the first time implemented for the reactions of *o*-keto phenols. This adds the 2,5-epoxybenzoxacine core to the previously obtained 2,5-epoxybenzazocine cores and offers rapid access to primary photoproducts which lend themselves to diverse yet simple postphotochemical modifications to further grow the complexity of the target structures, specifically – access to polyheterocycle-carbohydrate chimeras containing up to five contiguous stereogenic centers and benzazocine or benzoxacine heterocyclic cores.

Keywords: epoxybenzazocine; epoxybenzoxacine; photoassisted synthesis; Photochemistry XXVI; polyheterocycle-carbohydrate chimeras.

Introduction

We have developed a powerful synthetic methodology based on photoinduced generation of triplet aza-*o*-xylylenes which allows for rapid access to complex 2,5-epoxybenzazocines [1], and their subsequent postphotochemical modifications [2, 3]. The benzazocine core was previously reported as an intermediate in synthesis of mitomycinoid alkaloids [4], and was found in the structures of several alkaloids of the mitomycine family, such as FR-66979 and FR-900482, as well as their semi-synthetic analogues, FK-973 and FK-317 [5].

The oxygen-containing counterpart, 2,6-epoxybenzoxacine, is encountered in several anthracycline antibiotics, including nogalamycin (Fig. 1), and was a target of several synthetic and methodological studies [6]. Although nogalamycin was known for over half a century [7], no total synthesis of this natural product was reported so far, and there were only two total syntheses of its semisynthetic derivative, menogaril [8]. Most of the synthetic efforts were focused on the formation of the unique epoxybenzoxacine DEF ring system, which is thought to be responsible for DNA intercalation with the aminosugar forming two hydrogen bonds with DNA [9]. We were intrigued by the possibility of constructing 2,5-epoxybenzoxacine core via fewer steps

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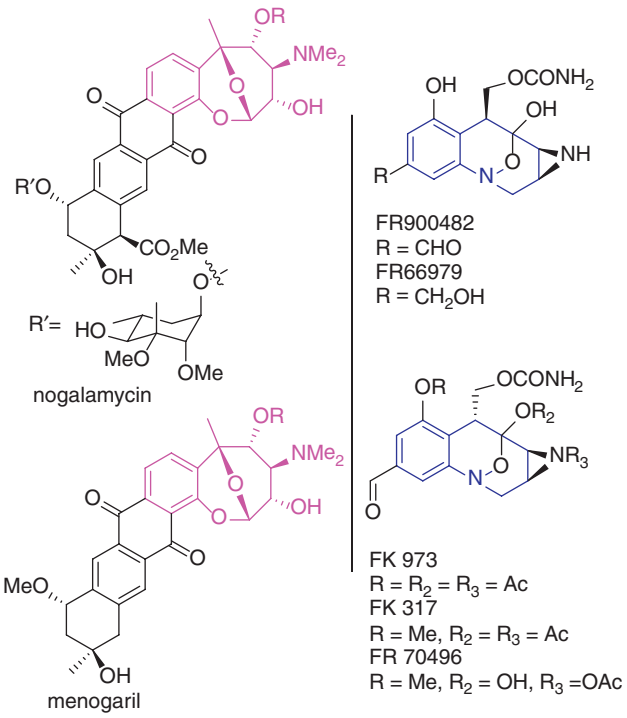


Fig. 1: Nogalamycin and related compounds.

taking advantage of photochemical excited state intramolecular proton transfer, and we embarked on this study with two goals (i) to determine the feasibility of benzoxacine ring formation by photochemical methods and (ii) to expand the methodology available for systematic functionalization of 2,5-epoxybenzazocines, and specifically hydroxylation with the ultimate goal of accessing noglamycine congeners.

It should be noted that even though the photochemistry and photophysics of aromatic *o*-hydroxy aldehydes, ketones [10], as well as esters [11] and imines [12] has been studied extensively, and excited state intramolecular proton transfer (ESIPT) in these species was known, there were no reports of synthetic utilization of the transient species, terminal C-hydroxy quinomethides. This is probably because of their short life time due to the back proton transfer. At the same time quinomethides lacking the terminal hydroxy group, were generated via alternative methods, including photochemical dehydration, and were shown to react with unsaturated compounds via the [4 + 2] hetero-Diels-Alder reactions [13]. It appears that these reactions occur in the ground state and therefore, due to the orbital symmetry considerations, only the [4 + 2] channel is available, as no [4 + 4] product have ever been reported.

We rationalized that the generation of hydroxy-substituted quinomethides via ESIPT and their excited state intramolecular cycloadditions with tethered doubly unsaturated furanyl pendants could be synthetically appealing for two reasons: one gains access to 2,5-epoxybenzoxacines via the [4 + 4] cycloaddition in the triplet excited state and, at the same time, one introduces the hydroxy functionality in the same step, paving the way to complex polyheterocycle-carbohydrate chimeras. Additions of aza-o-xylylenes, previously studied in our group, provide rapid access to benzazocine cores. These could also be outfitted with multiple functional groups, including the hydroxy group, in postphotochemical modifications. In this paper we report on our progress toward polyheterocycle-carbohydrate chimeras: (i) novel photoassisted synthesis of benzoxacines via ESIPT in aromatic keto-phenols and, (ii) hydroxylation of the primary photoproducts of aza-*o*-xylylene cycloadditions, i.e. benzazocines, allowing for systematic sampling of stereochemical diversity in these complex polyheterocyclic molecular architectures containing five contiguous stereogenic centers.

Experimental

Common solvents were purchased from Pharmco or Fisher Scientific and used as is, except for THF, which was refluxed over and distilled from sodium benzophenone ketyl prior to use. Common reagents were purchased from Aldrich and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25 °C on a Bruker Avance III 500 MHz in $CDCl_3$ (unless noted otherwise). High resolution mass spectra were obtained on the *Waters Synapt G2 ESI-MS* mass spectrometer from the University of Colorado at Boulder. Flash column chromatography was performed using Teledyne Ultra Pure Silica Gel (230–400 mesh) on a Teledyne Isco Combiflash R_f using hexanes/ethyl acetate as an eluent.

Synthesis of photoprecursors

(*E*)-3-(2-(Furan-2-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (3)

0.50 g (3.14 mmol) of 2-(furan-2-yl)benzaldehyde (**2**) was dissolved in 3 mL of ethanol, 0.43 g (3.16 mmol) of *o*-hydroxyacetophenone (**1**) was added, followed by the addition of 1 mL of 20 % aqueous NaOH. The reaction mixture was brought to reflux, at which it was maintained for 10 min. Upon cooling, the precipitated product was filtered yielding 0.70 g (77 %) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.86 (s, 1H), 8.39 (d, J = 15.3 Hz, 1H), 7.98 (dd, J = 8.1, 1.6 Hz, 1H), 7.78 (m, 2H), 7.62 (m, 2H), 7.53 (m, 2H), 7.42 (m, 1H), 7.07 (dd, J = 8.4, 1.2 Hz, 1H), 6.98 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 6.57 (m, 2H).

3-(2-(Furan-2-yl)phenyl)-1-(2-hydroxyphenyl)-4-nitrobutan-1-one (4)

0.30 g (1.03 mmol) of (*E*)-3-(2-(furan-2-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**3**) was dissolved in 3 mL of DMSO, 2 mL of nitromethane was added followed by the addition of 0.11 g of *t*BuOK. The reaction mixture was stirred overnight, quenched with aqueous NH_4Cl, extracted with ethyl acetate (three times), washed with brine and water, dried over Na_2SO_4 and concentrated to give 0.30 g (83 %) of product 4 which was used without additional purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.98 (s, 1H), 7.72 (dd, J = 8.1, 1.6 Hz, 1H), 7.55 (m, 2H), 7.50 (ddd, J = 8.7, 7.1, 1.6 Hz, 1H), 7.36 (m, 3H), 6.99 (dd, J = 8.5, 1.1 Hz, 1H), 6.91 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 6.62 (dd, J = 3.3, 0.8 Hz, 1H), 6.55 (dd, J = 3.3, 1.9 Hz, 1H), 4.81 (m, 3H), 3.58 (dd, J = 17.5, 6.0 Hz, 1H), 3.50 (dd, J = 17.5, 7.2 Hz, 1H). HRMS (ESI) calcd for $C_{20}H_{17}NO_5Li^+$ (M Li^+) 358.1261, found 358.1267.

α-Bromo-*o*-hydroxyacetophenone (5)

A round-bottom flask was charged with copper(II) bromide (4.91 g, 22.0 mmol), and ethyl acetate (20 mL) was added. 2-Hydroxyacetophenone **1** (1.50 g, 11.0 mmol) was dissolved in hot chloroform (10 mL) and added to the flask. The resulting reaction mixture was refluxed overnight, the copper(I) bromide was removed by filtration and the filter cake was washed well with ethyl acetate. The solvents were removed *in vacuo* and the concentrated material was diluted with ethyl acetate (60 mL) and washed with copious amounts of water until a neutral pH was achieved. The organic layer was washed with brine, dried over anhydr. Na_2SO_4, filtered, and concentrated yielding 2.23 g (94 %) of product used in further steps without additional purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.76 (s, 1H), 7.78 (dd, J = 8.1, 1.7 Hz, 1H), 7.56 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.06 (dd, J = 8.4, 1.1 Hz, 1H), 6.97 (m, 1H), 4.48 (s, 2H) [14].

2-(2-Bromoacetyl)phenyl *tert*-butyl carbonate (6)

To a solution of 2-bromo-2′-hydroxyacetophenone (**5**) (1.00 g, 4.65 mmol) and Boc_2O (2.23 g, 10.2 mmol) in hexanes (13 mL) and THF (4 mL) was added DMAP (0.085 g, 0.7 mmol, 15 mol%). The mixture was allowed

to stir overnight, then diluted with ethyl acetate (100 mL) and quenched with a mixture of 1 M HCl (42 mL) and brine (42 mL). The organic layer was separated, washed with $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated yielding 1.19 g (81 %) used in further steps without additional purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.8, 1.7 Hz, 1H), 7.61 (m, 1H), 7.36 (m, 1H), 7.31 (dd, J = 8.2, 1.2 Hz, 1H), 4.48 (s, 2H), 1.60 (s, 9H).

tert-Butylfuran-2-ylmethyl(2-(2-hydroxyphenyl)-2-oxoethyl)carbamate (8)

To a mixture of furfuryl amine **7** (0.57 g, 5.9 mmol) and DIPEA (1.1 mL, 6.3 mol) in DCM (19 mL) was added 2-(2-bromoacetyl)phenyl *tert*-butyl carbonate (**6**), (0.70 g, 2.22 mmol) in DCM (13 mL). The mixture was allowed to stir overnight, quenched with water (50 mL), the organic layer was separated, and the aqueous layer was additionally extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was subjected to flash chromatography (hexane-ethyl acetate) yielding 0.20 g (27 %) of the title compound as two amide rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.92 (m, 1H), 7.69 (m, 1H), 7.51 (m, 1H), 7.38 (m, 1H), 7.03 (m, 1H), 6.92 (m, 1H), 6.34 (m, 1H), 6.26 (m, 1H), 4.69 (m, 2H), 4.56 (m, 2H), 1.41 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 200.4, 162.3, 155.5, 155.3, 151.2, 151.0, 142.5, 142.4, 136.7, 128.9, 128.6, 119.1, 118.7, 118.6, 118.1, 117.9, 110.4, 110.3, 108.8, 108.2, 80.9, 80.7, 51.8, 51.5, 44.4, 43.9, 28.3, 28.2, HRMS (ESI) calcd for $C_{18}H_{21}NNaO_5^+$ (MNa^+) 354.1312, found 354.1321.

Irradiation of phenol photoprecursors

10-(Nitromethyl)-4,8b,9,10-tetrahydro-3H-3,14b-epoxybenzo[b]naphtho[2,1-d]oxacin-8b-ol (9)

0.36 g of 3-(2-(Furan-2-yl)phenyl)-1-(2-hydroxyphenyl)-4-nitrobutan-1-one (**4**) was dissolved in 300 mL of benzene, degassed and irradiated with RPR-3500 until completion as determined by NMR. 0.07 g (20 %) of the title compound was isolated after flash chromatography ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, J = 8.1, 1.7 Hz, 1H), 7.44 (ddd, J = 6.1, 4.6, 2.7 Hz, 1H), 7.36 (m, 3H), 7.26 (m, 1H), 7.10 (ddd, J = 8.3, 7.1, 1.4 Hz, 1H), 6.96 (dd, J = 8.1, 1.4 Hz, 1H), 6.73 (d, J = 5.9 Hz, 1H), 6.43 (d, J = 1.3 Hz, 1H), 6.11 (dd, J = 5.9, 1.4 Hz, 1H), 4.87 (dd, J = 12.5, 4.8 Hz, 1H), 4.54 (dd, J = 12.5, 9.6 Hz, 1H), 4.13 (m, 1H), 2.45 (dd, J = 14.2, 9.4 Hz, 1H), 2.27 (dd, J = 14.2, 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 137.8, 134.9, 134.5, 132.5, 129.6, 129.5, 129.1, 128.5, 128.0, 127.9, 127.3, 122.7, 121.6, 104.2, 90.3, 82.6, 81.4, 77.2, 38.1, 34.2. HRMS (ESI) calcd for $C_{20}H_{17}NNaO_5^+$ (MNa^+) 374.0999, found 374.1006.

N-*tert*-Butoxycarbonyl 7-aza-3,4-benzo-5-hydroxy-2,12-dioxa-tricyclo[7.2.1.0^{5,9}]dodeca-3,10-diene (10)

tert-Butyl furan-2-ylmethyl(2-(2-hydroxyphenyl)-2-oxoethyl)carbamate (**8**) (0.27 g, 0.81 mmol) was dissolved in MeOH (500 mL), degassed and irradiated (RPR-3500) until completion as determined by NMR. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography yielding (0.12 g, 44 %) of the title compound as two amide rotamers as determined by NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.07 (m, 2H), 6.92 (m, 1H), 6.46 (m, 1H), 6.35 (m, 1H), 5.74 (m, 1H), 4.14 (m, 1H), 3.86 (m, 1H), 3.76 (m, 2H), 3.34 (m, 1H), 1.53 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 154.4, 152.1, 152.0, 142.5, 142.3, 137.4, 137.3, 130.1, 130.0, 127.3, 127.2, 125.0, 124.9, 123.7, 123.5, 122.5, 122.4, 104.5, 104.5, 92.9, 92.5, 85.1, 84.4, 80.2, 80.1, 54.1, 53.7, 48.5, 48.0, 28.5, 28.4. HRMS (ESI) calcd for $C_{18}H_{21}NNaO_5^+$ (MNa^+) 354.1312, found 354.1325.

General procedure for dihydroxylation

1.2 mmol, 1 eq of the primary photoproduct was dissolved in 10 mL of acetone. To it 6.17 mmol, 5.1 eq of NMO in 0.7 mL of H_2O was added. After stirring for 15 min, 0.061 g of OsO_4 (0.24 mmol) was added, and the mixture was then stirred at the ambient temperature for 24 h. The reaction mixture was quenched with water, extracted with ethyl acetate, the combined organic layers were dried over anhydr. Na_2SO_4, and the residue was purified by flash chromatography.

12,14,15-Trihydroxy-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6(7),8(9),10(11)-trien-4-one (13)

From 300 mg (1.2 mmol) of primary photoproduct **12**, 0.76 g (6.1 mmol) of NMO, 0.061 g of OsO_4 90 mg (26 %) of the title compound was obtained ^{1}H NMR (500 MHz, MeOD) δ 7.41 (m, 3H), 7.29 (m, 1H), 4.70 (dd, *J* = 4.5, 1.0 Hz, 1H), 4.44 (dd, *J* = 4.6, 1.0 Hz, 1H), 3.79 (m, 2H), 2.92 (m, 1H), 2.61 (dtd, *J* = 13.5, 9.7, 1.1 Hz, 1H), 2.53 (m, 1H), 2.24 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 173.4, 135.8, 135.1, 132.9, 128.5, 128.4, 126.4, 104.5, 86.5, 75.3, 74.3, 72.2, 29.9, 27.8. HRMS (ESI) calcd for $C_{14}H_{15}NNaO_5^+$ (MNa^+) 300.0842, found 300.0850.

12,14,15-Trihydroxy-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6(7),8(9),10(11)-trien-4-one (15)

From 300 mg (1.2 mmol) of primary photoproduct **14**, 0.76 g of (1.6 mmol), NMO, 0.061 g of OsO_4 120 mg (35 %) of the title compound was obtained ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.12 (d, *J* = 9.8 Hz, 1H), 6.07 (dd, *J* = 9.8, 5.0 Hz, 1H), 5.31 (s, 1H), 5.16 (d, *J* = 5.0 Hz, 1H), 2.75 (m, 2H), 2.47 (ddd, *J* = 12.8, 7.7, 5.0 Hz, 1H), 2.40 (dt, *J* = 13.6, 10.0 Hz, 1H). ^{13}C NMR (126 MHz, MeOD) δ ^{13}C NMR (126 MHz, MeOD) δ 174.6, 133.7, 131.3, 129.2, 128.8, 125.5, 123.2, 98.5, 94.2, 73.5, 68.5, 55.3, 36.3, 29.3, HRMS (ESI) calcd for $C_{14}H_{15}NNaO_5^+$ (MNa^+) 300.0842, found 300.0849.

endo-cis,trans-13,14,15-Trihydroxy-16-oxa-5-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6(7),8(9),10(11)-trien-4-one (17)

From 0.25 mg (1.02 mmol) of compound **16**, 0.6 g (5.14 mmol) of NMO, 0.051 g of OsO_4, 148 mg (52 %) of the title compound was obtained ^{1}H NMR (500 MHz, MeOD) δ 8.51 (d, *J* = 8.3 Hz, 1H), 7.22 (m, 1H), 7.13 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.06 (td, *J* = 7.4, 1.2 Hz, 1H), 4.90 (m, 1H), 4.08 (d, *J* = 4.7 Hz, 1H), 3.97 (t, *J* = 2.3 Hz, 1H), 3.88 (m, 1H), 2.88 (ddd, *J* = 16.8, 11.3, 9.3 Hz, 1H), 2.51 (m, 1H), 2.46 (m, 1H), 2.20 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 174.9, 135.3, 127.0, 124.4, 123.6, 122.7, 117.7, 91.0, 75.6, 74.5, 71.2, 70.4, 33.3, 30.9, HRMS (ESI) calcd for $C_{14}H_{15}NNaO_5^+$ (MNa^+) 300.0842, found 300.0838.

exo-cis,cis-13,14,15-Trihydroxy-16-oxa-5-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6(7),8(9),10(11)-trien-4-one (22)

Triol **13** (13 mg, 0.46 mmol) was dissolved in 0.4 mL DMSO-d6 and heated to ~140 °C for 24 h. ^{1}H NMR monitoring revealed quantitative conversion to **22**. Solution was evaporated, product **22** was re-dissolved in methanol-d_4: ^{1}H NMR (500 MHz, MeOD) δ 8.54 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.31 (ddd, *J* = 8.6, 7.4, 1.7 Hz, 1H), 7.20 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.13 (td, *J* = 7.5, 1.2 Hz, 1H), 5.09 (d, *J* = 2.7 Hz, 1H), 3.88 (td, *J* = 3.0, 1.5 Hz, 1H), 3.77 (dd, *J* = 3.6, 1.6 Hz, 1H), 3.42 (t, *J* = 3.4 Hz, 1H), 2.95 (ddd, *J* = 12.8, 8.6, 1.2 Hz, 1H), 2.71 (ddd, *J* = 17.3, 12.1, 8.7 Hz, 1H), 2.52 (ddd, *J* = 17.4, 9.9, 1.2 Hz, 1H), 2.02 (td, *J* = 12.5, 9.8 Hz, 1H), ^{13}C NMR (126 MHz, MeOD) δ 173.7, 134.5, 128.1, 124.9, 123.5, 122.6, 117.7, 93.3, 77.4, 73.4, 72.5, 62.8, 29.0, 28.3.

18,19-Dihydroxy-20-oxa-3,9-diazapentacyclo[15.2.1.0^{1,9}.0^{3,7}.0^{10,15}]icosa-10,12,14-triene-2,8,16-trione (20)

From 320 mg (1.0 mmol) of primary photoproduct **18**, 0.6 g (5.1 mmol) of NMO, 0.05 g of OsO_4 100 mg (28 %) of the title compound was obtained ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.63 – 7.55 (m, 2H), 7.48 (dd, J = 8.3, 1.1 Hz, 1H), 7.36 (td, J = 7.5, 1.1 Hz, 1H), 4.99 (s, 1H), 4.74 (d, J = 5.7 Hz, 1H), 4.68 (dd, J = 5.7, 1.0 Hz, 1H), 4.62 (dd, J = 9.3, 7.3 Hz, 1H), 3.69 (dd, J = 9.0, 5.2 Hz, 2H), 2.50 (dtd, J = 13.7, 6.9, 2.9 Hz, 1H), 2.39 – 2.28 (m, 1H), 2.15 (ddt, J = 10.1, 5.0, 2.7 Hz, 1H), 2.05 (dddd, J = 15.0, 9.0, 7.3, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 202.6, 170.1, 163.4, 135.3, 132.8, 130.6, 129.1, 127.3, 126.1, 97.8, 92.6, 80.6, 75.3, 60.3, 45.1, 28.5, 22.6. HRMS (ESI) calcd for $C_{17}H_{16}N_2NaO_6^+$ (MNa^+) 367.0901, found 367.0889.

12,14,15-Trihydroxy-16-oxa-5,3-diazatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6(7),8(9),10(11)-trien-2,4-dione (21)

From 250 mg (0.91 mmol) of primary photoproduct **19**, 0.532 g (4.55) of NMO, 0.056 g of OsO_4 120 mg (47 %) of the title compound was obtained ^{1}H NMR (500 MHz, DMSO) δ 11.47 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 5.39 (d, J = 5.4 Hz, 1H), 5.24 (s, 1H), 4.76 (d, J = 7.6 Hz, 1H), 4.10 (s, 1H), 3.87 (t, J = 6.7 Hz, 1H), 3.55 (t, J = 5.6 Hz, 1H), 3.34 (s, 1H), 1.63 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ ^{13}C NMR (126 MHz, DMSO) δ 167.1, 153.3, 137.0, 134.1, 128.5, 128.3, 126.5, 126.0, 96.0, 93.2, 75.9, 74.1, 72.5, 26.3, HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_6^+$ (MNa^+) 329.0744, found 329.0746.

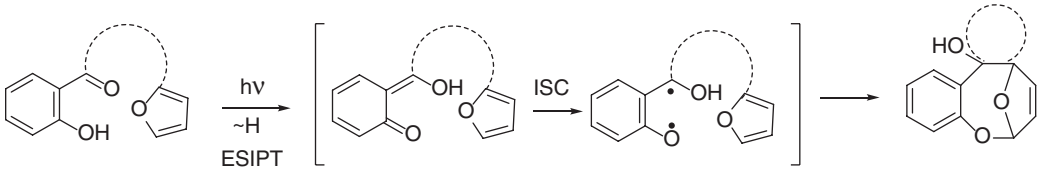
Results and discussion

We first discuss our approach to the benzoxacine core. The overall strategy is to utilize ESIPT in *o*-keto phenols and capture the transient triplet quinomethide intramolecularly with a heterodienic unsaturated pendant, furan, tethered via the keto-arm of the phenol as shown in Scheme 1. Our hypothesis is that ESIPT occurs very fast in the singlet manifold, followed by intersystem crossing into the triplet quinomethide, which is better represented as a 1,4-diradical.

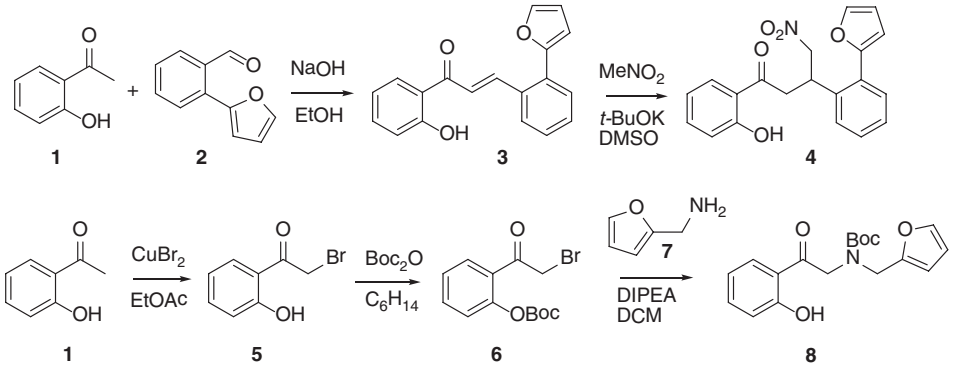
We considered two alternative synthetic approaches to the photoprecursors containing the requisite unsaturated pendant: (i) aldol condensation with *o*-hydroxyacetophenone **1**, and (ii) nucleophilic substitution in α-halogen substituted hydroxyacetophenone **5**. As shown in Scheme 2 the aldol condensation with 2-furylbenzaldehyde **2** is followed by Michael addition to the α,β-unsaturated ketone **3**. These are not high yielding reactions, but they are simple and could be implemented on a multigram scale.

The second approach to the photoprecursor is based on tethering the nucleophilic unsaturated pendant (i.e. furfurylamine) via nucleophilic substitution in α-halo acetophenones. Bromination of hydroxyacetophenone **1** with copper(II) bromide was followed by the Boc-protection of the phenol hydroxyl group and nucleophilic substitution of bromine with furfuryl amine **7**. Conveniently, the last step was accompanied by the simultaneous transfer of the Boc-group to the secondary amine moiety, yielding the photoprecursor **8** in just three simple steps from inexpensive commercially available materials.

Both phenol-containing photoprecursors exhibit relatively strong absorption around 365 nm and therefore are amenable to irradiation with the in-house built UV-LED illuminators (2.9 W @ 365 nm). Such



Scheme 1: General approach to benzoxacine cores via the ESIPT-generated quinomethide intermediate.



Scheme 2: Two approaches to photoprecursors.

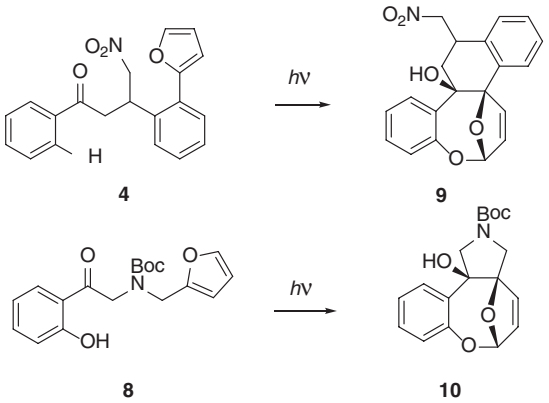
irradiation produced [4 + 4] cycloadducts. It should be noted that even though the photophysical properties of aromatic 2-hydroxyketones and aldehydes were well studied, and ESIPT in this systems is well-documented, the reactions depicted in Scheme 3 to the best of our knowledge are the first example of aromatic *o*-hydroxyketones participating in [4 + 4] cycloaddition reactions via quinomethane intermediates.

The second part of this study was to take advantage of the dihydroxylation reaction in primary photoproducts and create polyheterocycle-carbohydrate chimeras. Earlier we reported dihydroxylation of the double bond in 2,5-epoxybenzazocines [3], we now extend this procedure to other azocine- and quinolinole-containing molecules, i.e. both [4 + 4] and [4 + 2] primary photoproducts of intramolecular azaxylylene additions to a tethered furan moiety. In both cases (i.e. the [4 + 4] and [4 + 2] products of the model photoprecursor **11**) osmium tetroxide approaches from the less hindered "exo" side yielding triol aminals **13** and **15** with high stereoselectivity (Scheme 4). The structure of the products was unambiguously elucidated with X-ray analysis.

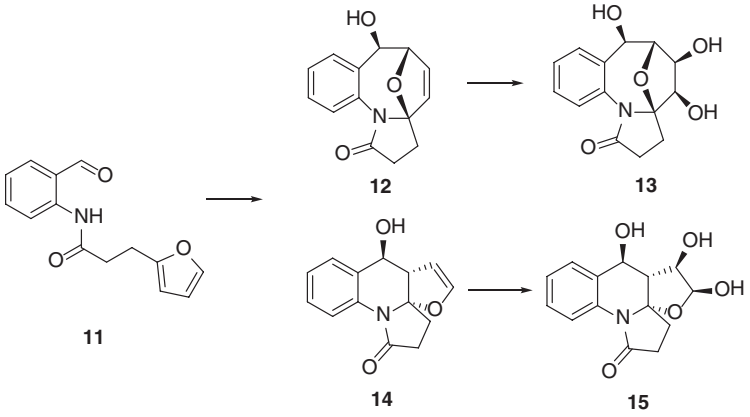
Contrary to this stereochemical outcome, dihydroxylation of 2,6-epoxybenzazocines, obtained from the corresponding 2,5-analogues by heating in DMSO solution or by the action of the acid (Scheme 5) clearly resulted from the endo-attack of osmium tetroxide.

This stereochemical outcome persists, i.e. the primary [4 + 4] photoproducts **18–19** also exhibited *exo*-selectivity of dihydroxylation, producing complex heterocycle-carbohydrate chimeras with well-defined carbohydrate-like contiguous *oxygenated* stereogenic centers (Scheme 6). Diol **20**, obtained from the L-proline-based photoproduct **18**, is enantiopure.

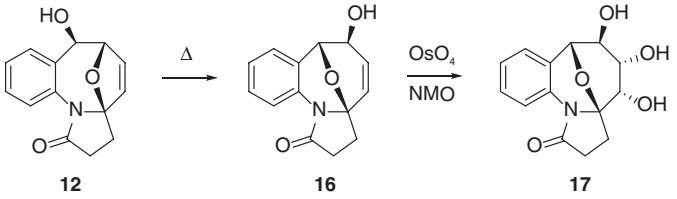
Instructively, analysis of transformations available for primary photoproducts led us to hypothesize that two well-defined diastereomeric 1,2,3-triols can be obtained by simply changing the order of the oxidation



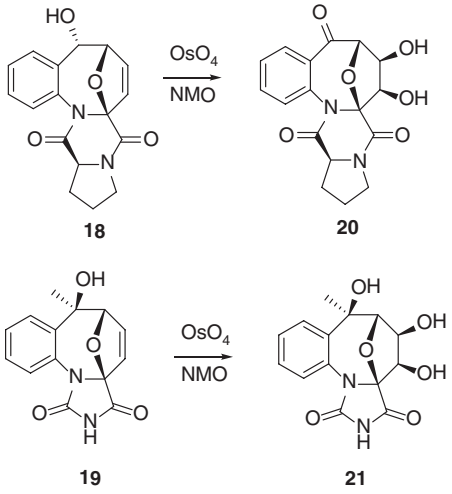
Scheme 3: Photoassisted access to benzoxacine cores via ESIPT in *o*-keto phenol photoprecursors **4** and **8**.



Scheme 4: Stereoselective *exo* dihydroxylation in the model system – both the [4 + 4] and [4 + 2] products **12**, **14**.



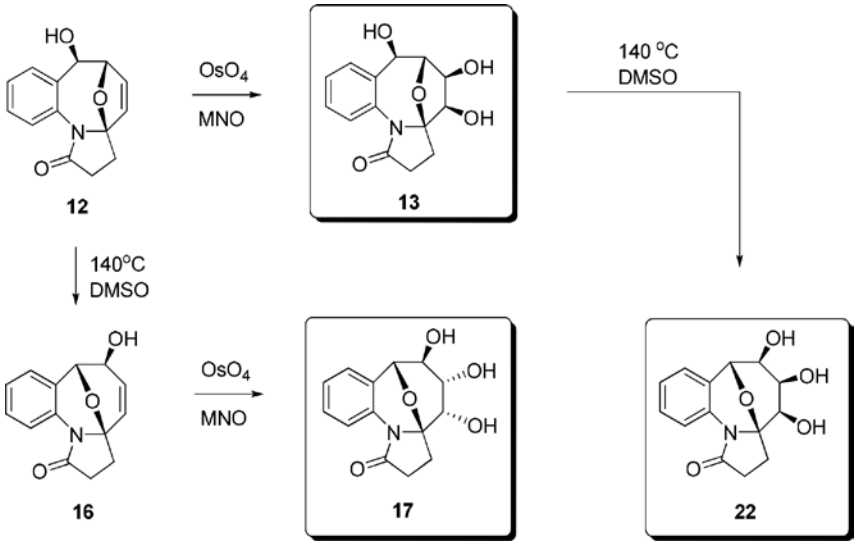
Scheme 5: Stereoselective *endo* dihydroxylation of the rearranged **16**.



Scheme 6: Additional examples of stereoseletive *exo*-dihydroxylation of the [4 + 4] primary photoproducts **18**–**19**. Proline-based diol **20** is enantiopure.

reaction and the bicyclo[4.2.1] → [3.3.1] rearrangement (i.e. 2,5-epoxy- to 2,6-epoxybenzazacines). Scheme 7 illustrates this point for the primary [4 + 4] photoproduct **12**. As already mentioned its direct dihydroxylation leads to the *exo* alcohol **13**, while the [4.2.1] → [3.3.1] rearrangement to **16** with subsequent oxidation yield the *endo* product **17**, possessing the oxazabicyclo[3.3.1]nonane core. However, heating of the triol **13** is accompanied by the same furanose-to-pyranose-form transformation (i.e. [4.2.1] → [3.3.1] rearrangement) yielding **22** as an all-cis diastereomer of the triol **17**.

This approach allows for systematic sampling of the stereochemical space in benzazocines, with fused pyrrolidone moiety, possessing five contiguous stereogenic centers. One can readily envision that this



Scheme 7: Primary photoproduct **12** exemplifies stereoselective access to diastereomeric 1,2,3-triol aminals **17** and **22**.

systematic approach can be extended via epoxidation of benzazocines **12** and **16** to access other diastereomers in this series, following the formation of an *anti*-diol fragment from oxirane ring-opening. Work is in progress in our labs to further extend this systematic methodology.

In conclusion, we extended the scope of ESIPT-induced cycloadditions to ortho-hydroxyketones, offering rapid access to benzoxacines, which are novel internal phenol glycosides. We also demonstrated synthetic utility of 1,2-dihydroxylation of the reactive double bonds both in [4+2] and [4+4] primary photoproducts producing heterocycle-carbohydrate chimeras and allowing for systematic sampling of stereochemical and chemical space.

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References

[1] (a) O. A. Mukhina, N. N. B. Kumar, T. M. Arisco, R. A. Valiulin, G. A. Metzel, A. G. Kutateladze. *Angew. Chem., Int. Ed*. **50**, 9423 (2011); (b) O. A. Mukhina, N. N. B. Kumar, T. M. Cowger, A. G. Kutateladze. *J. Org. Chem*. **79**, 10956 (2014); (c) O. A. Mukhina, D. M. Kuznetsov, T. M. Cowger, A. G. Kutateladze. *Angew. Chem. Int. Ed.* **54**, 11516 (2015); (d) O. A. Mukhina, A. G. Kutateladze. *J. Am. Chem. Soc.* **138**, 2110 (2016).

[2] (a) W. C. Cronk, O. A. Mukhina, A. G. Kutateladze. *J. Org. Chem*. **79**, 1235 (2014); (b) W. J. Umstead, O. A. Mukhina, A. G. Kutateladze. *Eur. J. Org. Chem.* **2015**, 2205 (2015); (c) W. J. Umstead, O. A. Mukhina, N. N. B. Kumar, A. G. Kutateladze. *Aust. J. Chem.* **68**, 1672 (2015).

[3] N. S. Nandurkar, N. N. B. Kumar, O. A. Mukhina, A. G. Kutateladze. *ACS Comb. Sci.* **15**, 73 (2013).

[4] For a review, see: P. D. Bass, D. A. Gubler, T. C Judd, R. M. Williams, *Chem. Rev.* **113**, 6816 (2013).

[5] S. E. Wolkenberg, D. L. Boger. *Chem. Rev.* **102**, 2477 (2002).

[6] (a) M. A. Bates, P. G. Sammes. *J. Chem. Soc. Chem. Commun.* **1983**, 896 (1983); (b) F. M. Hauser, W. P. Ellenberger, T. C. Adams, Jr., *J. Org. Chem.* **49**, 1169 (1984); (c) F. M. Hauser, T. C. Adam, Jr., *J. Org. Chem.* **49**, 2296 (1984); (d) R. P. Joyce, M. Parvez, S. M. Weinreb, *Tetrahedron Lett.* **27**, 4885 (1986); (e) T. H. Smith, H. Y. Wu. *J. Org. Chem.* **52**, 3566 (1987); (f) F. M. Hauser, W. P. Ellenberger. *J. Org. Chem*. **53**, 1118 (1988); (g) P. DeShong, W. Li, J. W. Kennington, Jr., H. L. Ammon. *J. Org. Chem*. **56**, 1364 (1991); (h) P. DeShong, W. Li, J. W. Kennington, Jr., H. L. Ammon. *J. Org. Chem*. **56**, 1364 (1991); (i) K. Krohn, H. J. Köhle Liebigs. *Ann. Chem.* **1987**, 1037 (1987); (j) M. Kawasaki, F. Matsuda, S. Terashima. *Tetrahedron* **44**, 5713 (1988); (k) M. Kawasaki, F. Matsuda, S. Terashima. *Tetrahedron* **44**, 5727 (1988); (l) F. M. Hauser, D. Ganguly. *J. Org. Chem.* **65**, 1842 (2000); (m) F. Matsuda, M. Kawasaki, M, Ohsaki, K, Yamada, S. Terashima. *Chem. Lett.* **1988**, 653 (1988); (n) M. Kawasaki, F. Matsuda, S. Terashima. *Tetrahedron* **44**, 5695 (1988); (o) R. P. Joyce, M. Parvez, S. M. Weinreb. *Tetrahedon Lett.* **27**, 4885 (1986);

(q) K. Krohn, V. S. Ekkundi, D. Doring, P. J. Jones. *Carbohyd. Chem*. **17**, 153 (1998); (r) K. Krohn, U. Florke, J. Keine, I. J. Terstiege. *Carbohyd. Chem*. **17**, 171 (1998); (s) K. Krohn, I. Terstiege, U. J. Florke. *Carbohyd. Chem*. **17**, 197 (1998); (t) Y. Htwe, R. W. Franck, S. L. Chen, G. J. Quigley, L. Todaro. *J. Org. Chem*. **57**, 644 (1992); (u) R. Peng, M.S. VanNieuwehnze. *Org. Lett*. **14**, 1962 (2012).

[7] P. F. Wiley, F.A. Mackellar, E. L. Caron, R. B. Kelly. *Tetrahedron Lett*. **9**, 663 (1968).

[8] F. M. Hauser, S. CHakrapani, W. P. Ellenberger. *J. Org. Chem*. **56**, 5248 (1991); M. A. Bates, P. G. Sammes. *J. Chem. Soc. Perkin Trans*. **1**, 3037 (1988).

[9] (a) A. Rich, L. D. Williams, M. Egli, Q. Gao, P. Bash, G. A. V. D. Marel, J.H.V. Boom, C. A. Friedrick. *Proc. Natl. Acad. Sci. U.S.A*. **87**, 2225 (1990); (b) S.P. Sim, B. Gatto, C. Yu, A. A Liu, T. K. Li, D. S. Pilch, E. J. LaVoie, L. F. Liu. *Biochemistry* **36**, 13285 (1997); (c) Y. C. Liaw, Y. G. Gao, H. Robinson, G. A. Vandermarel, J. H. Vanboom, A. H. J. Wang. *Biochemistry* **28**, 9913 (1989); (d) S. P. Sim, D. S. Pilch, L. F. Liu, *Biochemistry* **39**, 9928 (2000).

[10] (a) S. K. Ketones, G. K. Sarkar, R. A. A. U. Weragoda, A. D. Ranaweera, Gudmundsdottir. *J. Phys. Chem. B*. **119**, 2668 (2015); (b) A. Deperasinska, M. Makarewicz, D. T. Krzeszewski, B. Gryko, Kozankiewicz. *J. Phys. Chem*. **119**, 9051 (2015); (c) M. H. Van Benthem, G. D. Gillispie. J. *Phys. Chem*. **88**, 2954 (1984); (d) S. R. Flom, P. F. Barbara. *J. Phys. Chem*. **89**, 4489 (1985).

[11] (a) J. Esters, Catalán. *Phys. Chem. Chem. Phys*. **14**, 8903 (2012); (b) J. Catalán *J. Phys, Chem. B*. **119**, 2132 (2015); (c) P. Zhou, M. R. Hoffmann, G. He, *J. Phys. Chem. B*. **119**, 2125 (2015).

[12] (a) P. F. Imines, L. E. Barbara, P. M. Brus, Rentzepis *J. Am. Chem. Soc*. **102**, 2786 (1980); (b) K. Ding, S. H. A. J. Courtney, S. Stranjord, D. Flom, P. F. Friedrich Barbara. *J. Phys. Chem*. **87**, 1125 (1983).

[13] (a) S. Arumugam, S. V. Orski, J. Locklin, V. V. Popik. *J. Am. Chem. Soc*. **134**, 179 (2012); (b) S. Arumugam, V. V. Popik. *J. Am. Chem. Soc*. **133**, 5573 (2011); (c) S. Arumugam, V. V. Popik. *J. Am. Chem. Soc*. **133**, 15730 (2011); (d) S. Arumugam, V. V. Popik. *J. Am. Chem. Soc*. **131**, 11892 (2009).

[14] B. P. Ngoy, P. Šebej, T. Šolomek, B. H. Lim, T. Pasterik, B. S. Park, R. S. Givens, D. Heger, P. Klán. *Photochem. Photobiol. Sci*. **11**, 1465 (2012).